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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/464,414	12/16/1999	YASMIN THANAVALA	RPP:156CUS	7502

7590 04/22/2002

DUNN & ASSOCIATES
P O BOX 96
NEWFANE, NY 14108

EXAMINER	
FLOOD, MICHELE C	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 04/22/2002 19

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/464,414	Applicant(s) Thanavala
	Examiner Michele Flood	Art Unit 1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 25, 2002* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-3, 7, 9, 10, 12, and 13* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-3, 7, 9, 10, 12, and 13* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Acknowledgment is made of the receipt and entry of the amendments filed on January 25, 2002.

Claims 1-3, 7, 9-10, and 12-13 are under examination.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-3, 7, 9-10 and 12-13 as amended remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for providing a secondary boosting response in a mammal to a non-enteric pathogen antigen (NEPA), wherein the NEPA is hepatitis B surface antigen (HBsAg) comprising the instantly claimed process steps and instantly claimed ingredients, does not reasonably provide enablement for providing a secondary boosting response in a mammal to any and all NEPAs comprising the instantly claimed process steps and instantly claimed ingredients. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

and/or use the invention commensurate in scope with these claims. The rejection stands for the reasons set forth in the previous Office action and set forth below.

The claims are directed to a method for providing a secondary immune response in a mammal to a specific antigen of a non-enteric pathogen (NEPA), the pathogen being a pathogen that invades through a breach in the skin and that does not itself enterically raise a primary protective immune response in mammals in the absence of prior acquired immunity to the pathogen, said method comprising: rendering the mammal immunoreceptive to the NEPA by prior immunization against a non-enteric pathogen containing the NEPA by vaccination by injection; and then orally administering a NEPA to the immunoreceptive mammal by feeding the mammal with transgenic potato containing the NEPA expressed in the potato to enterically cause a secondary immune response to the oral administration specific to the NEPA stronger than would be caused by orally administering the NEPA in the absence or the prior immunization by injection. The claims are further drawn to a method where the mammal is human. The claims are further drawn to a method, wherein the NEPA is an antigen specific to a non-enteric pathogen selected from the group consisting of those that cause hepatitis B, hepatitis C, hepatitis delta, yellow fever, dengue hemorrhagic fever, tetanus, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever. The claims are further drawn to a method wherein the human ingests sufficient plant material to provide from about 10 to about 100 micrograms of NEPA per kilogram of body weight of the human, wherein the human ingests sufficient plant material to

provide from about 2 to about 5 grams of plant material per kilogram of body weight of the human, and wherein the human ingests said plant material a plurality of different times, said times being separated from each other by at least 5 days, wherein the plurality of times is three times.

Applicant argues that the rejection should be withdrawn since there is in fact clear enabling support in the specification, especially when considered in conjunction with the knowledge of one skilled in the art. Applicant's further arguments are directed to the main idea that one skilled in the art now knows how to cause a plant to express a viral immunogen in view of the cited prior art of record, in particular the teachings of US Patent 6,136,320 and US Patent 5,679,880. Thus, Applicant concludes that the rejection made by the Office should be withdrawn since the Office has relied upon patents that clearly teach how to make the required plant materials and that the cited patents have generically claimed such plant materials.

However, Applicant's arguments are not deemed persuasive, especially in view of the cited prior art made of record, because Applicant's arguments are mainly directed to the method of making the claim-designated plant material but not to the use thereof. For instance, the specification broadly discloses non-enteric pathogens that invade the epidermis of mammals via punctures, abrasions, cuts or other breaches in the skin, e.g. blood transfusions, which can be used as sources of NEPA to raise a protective enteric immune response in mammals. However, the specification does not provide sufficient guidance as to how one of ordinary skill in the art would

provide an immune response in a mammal and/or a human to a NEPA other than the non-enteric pathogen antigen, hepatitis B surface antigen. The specification does not disclose other specific non-enteric pathogen antigens which have been subjected to the claim-designated therapeutic regimen, nor does the specification teach any methodology associated with the making of genetically altered plant materials expressing any other NEPA other than the non-enteric pathogen antigen, hepatitis B surface antigen. In regard to Claim 1, the specification other than the mere suggestion on page 1, lines 13-16,does not provide guidance as to how to use the instantly claimed invention to provide a secondary [boosting] immune response to any and all diseases caused by a non-enteric pathogen that invade the epidermis of mammals via punctures, abrasions, cuts or other breaches in the skin. Moreover, there is inadequate guidance as to how one of ordinary skill in the art would use the instantly claimed invention to genetically alter potato plant material to express any and all non-enteric pathogens other than the exemplified HbsAg for use in the claim-designated method for raising the immune response in a mammal and/or human when administered orally.

Applicant's arguments to the idea that one skilled in the art would know how to "cause a plant to express a viral immunogen (antigen)", i.e., to make a genetically altered plant materials expressing a NEPA or pathogenic microorganism, is persuasive in view of the prior art teachings. However, Applicant's argument with regard to how one skilled in the art would know how to use any and all plant materials expressing any and all NEPAs in the instantly claimed method is not

persuasive, except for those demonstrated by Applicant, or disclosed by the teachings of the cited prior art (see Tables in Columns 13-14 in U.S. 5,914,123 and U.S. 6,136,320).

The art of virology, microbiology, and immunology are highly unpredictable because there are too many unknowns in the claimed process for the skilled artisan to be enabled to practice the invention commensurate in scope to the claimed invention. Effective treatments for providing immunological responses to the disclosed pathogens are relatively rare, and may be unbelievable in the absence of supporting evidence. Claims drawn to methods for the administration of compositions to mammals and/or humans generally require supporting evidence which clearly define the ingredients or constituents contained therein because of the unpredictability in biological responses to therapeutic treatments. In order to enable the skilled artisan to practice the invention as claimed, Applicants would have to demonstrate the functional effect and describe the effective amounts of each ingredient for the administration of the composition intended for a therapeutic treatment. Accordingly, it would take undue experimentation without a reasonable expectation of success to determine which amounts of the instantly claimed plant materials expressing a non-enteric pathogen selected from those pathogens which cause the diseases hepatitis C, hepatitis delta, yellow fever, dengue, hemorrhagic fever, tetanus, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever, other than the demonstrated hepatitis B, to provide the claimed functional effect to cause a secondary immune response in a mammal, wherein the specific immune response to the NEPA

was stronger than would be caused by the NEPA in the absence or prior immunization by rejection upon oral administration of the NEPA.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-3, 7, 9-10 and 12-13 as amended remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection stands for the reasons set forth in the previous Office and set forth below.

Applicant asserts that the amendment of Claim 1, line 2, has overcome the rejection made in the previous Office action, however, this is not persuasive because the phrase "to a specific antigen of a non-enteric pathogen (NEPA)" renders the claim vague and indefinite. It still remains unclear as to the meaning of the abbreviation. While the specification clearly defines the abbreviation "(NEPA)" as a "non-enteric pathogen antigen", on page 5, line 5, as drafted it appears that the term refers to a non-enteric pathogen. What does "A" stand for in the abbreviation (NEPA)? The lack of clarity makes the claim ambiguous and very confusing.

Applicant argues that any person skilled in the art knows what vaccination by injection means and that the ingredients comprised in the vaccination does not matter. However,

Applicant's argument is not commensurate in scope to the claimed invention. Thus, Claim 1, lines 5-7, is rendered vague and indefinite by the phrase "by prior immunization against a non-enteric pathogen containing the NEPA by vaccination by injection" because the phrase is very confusing. It is uncertain as to what is contained therein the injection. Does the injection comprise a non-enteric pathogen or NEPA, or both ? Applicant may overcome the rejection by better defining the subject matter of the claimed invention by detailing what comprises the vaccinating injection, as the metes and bounds are made uncertain by the lack of clarity.

Applicant argues that the "generic objection" with respect to grammatical and idiomatic errors cannot be addressed because the objection is not understood. Although, Applicant asserts to conform with current U.S. practice, the Office notes even as amended Claim 1 appears to contain a typographical error. For instance, while Applicant previously amended Claim 1 in Paper No. 12 (dated 2/2/01) to recite "A method for providing a secondary boosting immune response in a mammal, Claim 1 now recites "A method for providing a secondary immune response in a mammal." It appears that Applicant has omitted the term "boosting", but it is uncertain as to what Applicant claims as the "Version with markings to show changes made" in the current amendment of Paper No. 18 (dated 1/25/02) does not properly reflect any change to the claim language. In another instance, Applicant is pointed to Claim 1, lines 5-6, wherein the claim language recites the phrase "rendering the mammal immunoreceptive to the NEPA by injection". The phrase is generally narrative, confusing, vague and indefinite as all mammals are

immunoreceptive unless their immune system is somehow compromised, i.e., the mammal is immunodeficient. Thus, the rejection remains the same as set forth in the previous Office action of Paper No. 17 (dated July 17, 2001).

Applicant is, once again, advised that should claim 10 be found allowable, claim 12 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

All other claims depend directly or indirectly from rejected claims and are, therefore, also, rejected under U.S.C. 112, second paragraph for the reasons set forth above.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-3, 7, 9-10, and 12-13 as amended remain rejected under 35 U.S.C. 103(a) as being unpatentable over Arntzen et al. (A, US Patent 5,914,123) or Arntzen et al. (B, US Patent

6,136,320) in view of Stites (U), and further in view of readily admitted prior art. The rejection stands for the reasons set forth in the previous office action and set forth below.

Applicant's arguments have been fully considered but they are not deemed persuasive because the cited references provide the suggestions and motivation to the claimed invention.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the teachings of Arntzen (US Patent 5,914,123) was relied upon because '123 teaches methods of making a transgenic plant expressing an immunogen derived from hepatitis B surface antigen, wherein the immunogen is capable of eliciting an immune response in an animal by oral administration of the plant material. Arntzen also teaches methods of making a vaccine by recovering the immunogen expressed in the plant cell for use as a conventional injectable vaccine (see Claims 1-3 and 6). Moreover, Arntzen teaches that the transgenically altered plant material expressing the HBsAg can be used to both prime the mucosal immune system and/or stimulate the humoral immune response in a dose dependent manner. In Column 11, lines 36-50, Arntzen teaches that either the parenteral or non-parenteral introduction of the vaccine to a

mammal can elicit serum and/or secretory antibodies against the HBsAg immunogen of the vaccine with minimal induction of systemic tolerance. Finally, Arntzen teaches that a plurality of different administrations of the genetically altered plant material expressing the HBsAg over separate periods of time provide the claimed functional effect of raising the serum IgM and IgG response specific to the hepatitis B surface antigen to achieve a secondary immune response or immunization of a mammal. Note that Arntzen specifically teaches that the plurality of times for the administration of the vaccines is in a range of 3 to 6, and that the time separating the vaccinations is in a range of 14 to 35 days to achieve protective levels of antibodies. See Column 15, lines 45-61.

The reference of Arntzen (US Patent 6,136,320) was relied upon because '320 teaches an anti-viral vaccine which is produced in transgenic plants, and then administered through standard vaccine introduction method or through the oral consumption of the edible portions of the plant (see ABSTRACT). The transgenic plants used in the making of the vaccines taught by Arntzen include the potato plant (see Column 16, line 43-53), and the plants are used to express various non-enteric pathogen antigens, such as Hepatitis B antigen (see claims 8-10 and the table found in Column 13 and 14). In Column 15, lines 3-67 to Column 16, lines 1-3, Arntzen teaches that the vaccines of his invention can be used in the making of oral vaccines, as well as, traditional injectable vaccines. Finally, Arntzen teaches the administration of multiple vaccination doses at

varying intervals, as well as, periodic booster vaccinations to maintain protective levels of immunity.

Applicant argues that neither of the references of Arntzen et al. teach "methods of making a transgenic plant expressing an immunogen derived from hepatitis B surface antigen, wherein the immunogen is capable of eliciting an immune response in an animal by consumption of the plant material." Applicant further argues that the prior art does not teach how to make NEPAs raise an oral immune response; does not give any examples of ingestion of the referenced plant products to raise an immune response or to confer immunity; and, does not suggest preimmunization by injection followed by oral feeding of a transgenic potato expressing a NEPA to obtain a secondary immune response as required by the claimed invention. Applicant even argues, " . . . in fact the plants made in the examples do not function orally to raise an immune response to any NEPA." It appears that Applicant is asserting that the prior art U.S. patents are not valid. Prophetic statements cannot be used to form the basis of a sound argument, especially when they are unsupported and not true. Thus, Applicant's arguments are not persuasive because both '123 and '320 teach methods of making an edible transgenic plant product expressing (wherein the plants suitable for the referenced teachings include potato) an immunogen derived from a non-enteric pathogen, e.g., hepatitis B surface antigen; methods of administering the plant product through standard vaccination introduction method or through the consumption of the edible portions of the plant product; and, methods for the multiple administrations of the

referenced vaccines to provide an immunogenic response in the subject to which it is administered. *See* entire document of U.S. 5,914,123 and U.S. 6,136,320, including the claims.

Although Applicant argues that Stites does nothing to cure the inadequate teachings and suggestions of either '123 or '320, the reference of Stites was relied upon because Stites teaches the principles of immunization which can be applied to a variety of vaccine types. Stites, also, teaches that the timing of immunization, the interval between does, and the timing of booster reimmunization are based on both theoretic considerations and vaccine trials.

Thus with Arntzen ('123 and '320) providing the motivation to use transgenic potato plants expressing an immunogen derived from an non-enteric pathogen, e.g. Hepatitis B surface antigen, to elicit an immune response in a mammal comprising administration of the referenced product by either oral or traditional injection vaccination over a plurality of different and separate times to achieve a secondary immune response or immunizing effect, and with Stites teaching that the principles of immunization can be applied to a variety of vaccine types, it would have been obvious to one of ordinary skill in the art at the time the invention was made to provide a secondary [boosting] immune response in an individual wherein the individual ingests genetically altered potato plant product expressing an non-enteric pathogen antigen after a primary step of immunization by vaccine injection because it was old and well known in the art that reimmunization or a "booster shot" in a previously immune or primed individual provides a rapid secondary increase in immunity, as evidenced by the teachings of Stites.

Furthermore, it would have been obvious to one of ordinary skill and one would have been motivated with a reasonable expectation of success to combine the claimed method steps in a method for providing a secondary boosting immune response in a mammal and/or a human because it was well-known in the art, as readily admitted by applicant on page 3, lines 17-23 of the present specification that, "Plants expressing hepatitis B surface antigen (HBsAg) have in fact been developed but have also disappointingly been found to create little or unacceptably low immune responses in animals ingesting them even though HBsAg isolated from plants have been found to raise an immune response when administered parenterally"; and both teachings of Arntzen teach methods of eliciting an immunogenic response in an individual by administering the plant product vaccine either by oral or injection presentation.

As the references indicate the various ingredients, various proportions, and various times for the administration of a vaccine, they would have been routinely optimized by one of ordinary skill in the art practicing the invention disclosed by each of the references.

Accordingly, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

No claims are allowed.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele Flood whose telephone number is (703) 308-9432. The examiner can normally be reached on Monday through Friday from 7:15 am to 3:45 pm. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196 or the Supervisory Patent Examiner, Michael Wityshyn whose telephone number is (703) 308-4743.

MCF

April 18, 2002

CHRISTOPHER R. TATE
PRIMARY EXAMINER